Citation:

Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension.* 1997; 29: 913–917.

PubMed ID: 9095076

Study Design:

Randomized trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate whether contrasting levels of sodium intake during the first six months of life are still associated with blood pressure at age 15 years, and whether the effect of sodium is modified by sex, body mass index and resting heart rate.

Inclusion Criteria:

- Completed original trial studying the effect of sodium intake on blood pressure as an infant (N=466)
- Had a current addresses that could be traced
- Still lived in Zoetermeer
- Could be contacted by telephone
- Agreed to participate.

Exclusion Criteria:

None.

Description of Study Protocol:

Recruitment

Subjects of the original cohort (infants born in 1980 to healthy women living in Zoetermeer, Netherlands) were contacted after 15 years of follow-up.

Design

Randomized trial with 15-year follow-up.

Dietary Intake/Dietary Assessment Methodology

- The study protocol for the original trial with dietary intervention is described in previous publications
- The average daily amount of sodium (standard deviation) consumed in the trial was 0.89mol (0.26mol) in the low sodium group and 2.50mol (0.95mol) in the normal sodium group.

Blinding Used

- Original trial was double-blind
- Study personnel measuring blood pressure, height and weight at the 15-year follow-up were masked to subjects' original group assignment.

Intervention

Subjects were randomized as infants to either a low sodium diet or a normal sodium diet during the first six months of life.

Statistical Analysis

- Two-tailed unpaired T-test for difference in blood pressure after 15 years of follow-up
- Multiple linear regression to account for differences in study groups at follow-up.

Data Collection Summary:

Timing of Measurements

After 15 years of follow-up, blood pressure, heart rate, height, weight and an overnight urine sample were collected from subjects.

Dependent Variables

Systolic and diastolic blood pressure were measured on the right arm after five minutes of rest by two investigators using an automated device while the subject was seated; four measurements were made and the last three were averaged and used for the analyses.

Independent Variables

Original trial group of low or normal sodium diet.

Control Variables

- Sex, birth length and weight, maternal educational level, maternal systolic blood pressure at baseline, educational level of subject, presence of treated hypertension in parents, person measuring blood pressure
- Multiple regression model repeated with stratification by sex, body mass index (BMI) and resting heart rate.

Description of Actual Data Sample:

- *Initial N:* 466 subjects eligible from the original trial cohort
- *Attrition (final N):* 167 subjects (71 from the low sodium group and 96 from the normal sodium group)
- *Age:* 15 years
- *Anthropometrics:*

- At 15 years, subjects in the low sodium group had significantly less education and more had a parent currently treated for hypertension
- At baseline, infants in the low sodium group were greater in weight and length at birth, and had a mother with lower educational level and higher systolic blood pressure

- *Location:* Zoetermeer, Netherlands.

Summary of Results:

Blood Pressure Differences Between Low Sodium and Control Groups After 15 Years of Follow-up

Variables	Low-normal Sodium Group (95% Confidence Interval)	P-value (Two-sided)
Systolic blood pressure (mmHg)	-3.6 (-6.6, -0.5)	0.02
Diastolic blood pressure (mmHg)	-2.2 (-4.5, 0.2)	0.08

*Multivariate models adjusted for sex, birth length and weight, education, hypertension in parents, maternal education, maternal systolic blood pressure and blood pressure observers.

Differences in Blood Pressure (BP) at Follow-up Between Low Sodium and Control Groups Within Heart Rate (HR) Strata

Low HR indicates boys with HR of 76 beats per minute or less and girls with HR 83 beats per minute or less, According to median of sex-specific HR distribution at follow-up. High HR stratum includes subjects with higher HRs.

Variables	High HR Low-normal Sodium Group (95% Confidence Interval)	P-value (Two-sided)	Low HR Low-normal Sodium Group (95% Confidence Interval)	P-value (Two-sided)
Systolic blood pressure (mmHg)	-6.0 (-10.5, -1.5)	0.01	0.8 (?)	>0.05
Diastolic blood pressure (mmHg)	-4.8 (-8.7, -0.9)	0.02	1.7 (?)	>0.05

*Adjusted multivariate models.

Other Findings

Mother's systolic blood pressure was positively associated with child's blood pressure 15 years later.

Author Conclusion:

- Neonatal sodium intake could be related to blood pressure level in adolescence

- This long-term follow-up of a cohort of children exposed to contrasting levels of sodium intake during the first six months of life shows an association of sodium intake in infancy with systolic and diastolic blood pressures 15 years later in life only in children with a relatively high heart rate, after adjustment for confounders.

Reviewer Comments:

Strengths

Rigorous data analysis, taking potential confounders into account in a multiple linear regression model.

Limitations

The loss to follow-up of subjects, which introduced unequal distributions of baseline and follow-up characteristics between study groups.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	???

2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes

5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes

8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	N/A
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	Yes
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	???
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	N/A